2019 Endocrine and Diabetes Symposium for Primary Care Providers

Osteoporosis Case Studies

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Founder, Sierra Endocrine Associates Medical Group
Relevant Disclosures

- Speakers Bureau
  - Amgen
  - Radius

- Advisory Panel / Marketing Consulting
  - Amgen
The audience will learn how to diagnose osteoporosis.

The audience will learn how to assess fracture risk.

The audience will understand the risks and benefits of osteoporosis treatment and how to balance the two.
Osteoporosis: A Major Public Health Issue

“2-million-2 Many”

1/2 of women and up to 1/4 of men over age 50 will break a bone due to osteoporosis.

5,500 Fractures Daily

Over 1/3 of patients with a hip fracture had a prior fracture.

1/4 end up in nursing homes and 1/2 never regain previous function.

After a fracture, 4 out of 5 women over 67 are not tested or treated for osteoporosis.

50% of osteoporosis-related repeat fractures can be prevented with appropriate treatments.

Osteoporosis fractures will likely cost us $25 billion per year by 2025.

National Bone Health Alliance
Osteoporosis is a Common Condition in Women in the U.S.

Number of Events Annually in the US

Osteoporotic Fracture: 2,000,000\(^1\)
Heart Attack: 513,000\(^2\)
Stroke: 228,000\(^3\)
Breast Cancer: 184,300\(^4\)
Uterine Cancer: 34,000\(^4\)
Ovarian Cancer: 26,700\(^4\)

\(^1\) CDC, 2020
\(^2\) National Osteoporosis Foundation, 2020
\(^3\) American Heart Association, 2020
\(^4\) American Cancer Society, 2020
What are the Consequences of Underdiagnosing and Undertreating Osteoporosis?

In women with hip fracture:

- **Fracture begets future fracture**
- **Deteriorated quality of life**
- **Long-term care admission**
- **Mortality**

- 40% had prior fracture\(^1\)
- 40% need assistance walking\(^2\)
- 18% enter LTC\(^3\)
- 23% die within 1 year\(^4\)

\*Lifetime risk of hip fracture in women > 50 is 12.1%\(^5\)

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Osteoporosis is a systemic disease characterized by low bone mass & micro-architectural deterioration with a consequent increase in bone fragility and susceptibility to fracture.
Osteoporosis – Case 1

70 YO Caucasian Female

- PCP ordered a BMD screen – first time measured
- BMD – Lowest measured site in the Fem Neck T-score - 2.2
- She is a smoker and her mother has a history of a hip fracture

QUESTIONS?
1. Does she have osteoporosis?
2. How should patient be treated?
How do we Combine these Risks into a usable Fracture Risk Assessment?

- **WHO FRAX Risk Assessment Tool**
  - Incorporated into Bone Density Software
  - Available as a Smart Phone App
  - Available online: [http://www.shef.ac.uk/FRAX](http://www.shef.ac.uk/FRAX)
FRAX Fracture Risk Calculator

**Questionnaire:**
1. Age (between 40 and 90 years) or Date of Birth
   - Age: 70
   - Date of Birth: Y: _, M: _, D: _
2. Sex
   - Male
   - Female
3. Weight (kg)
   - 68
4. Height (cm)
   - 162.6
5. Previous Fracture
   - No
   - Yes
6. Parent Fractured Hip
   - No
   - Yes
7. Current Smoking
   - No
   - Yes
8. Glucocorticoids
   - No
   - Yes
9. Rheumatoid arthritis
   - No
   - Yes
10. Secondary osteoporosis
    - No
    - Yes
11. Alcohol 3 or more units/day
    - No
    - Yes
12. Femoral neck BMD (g/cm²)
    - T-Score: -2.2

**BMI: 25.7**
The ten year probability of fracture (%)

with BMD
- Major osteoporotic: 13%
- Hip Fracture: 2.9%

If you have a TBS value, click here: Adjust with TBS
FRAX Fracture Risk Calculator

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12. Femoral neck BMD (g/cm²)
    T-Score: -2.2

BMI: 25.7
The ten year probability of fracture (%)
with BMD

- Major osteoporotic: 23%
- Hip Fracture: 10%

If you have a TBS value, click here: Adjust with TBS
Criteria for a Diagnosis of Osteoporosis

1. In the Presence of a Fragility Fracture in lumbar spine, Femoral Neck, Hip in the absence of other metabolic bone disorders

2. BMD T-Score is – 2.5 or lower in any single ROI: Lumbar Spine, Femoral Neck, total hip or 33% radius even in the absence of prevalent fracture

3. Osteopenia or low bone mass (T-score between -1 and -2.5) with a fragility fracture of the proximal humerus, pelvis or distal forearm

4. Osteoporosis may also be diagnosed in patients with low bone mass (T-Score -1.0 to -2.4, “Osteopenia”) who are at Increased Fracture Risk using FRAX Country Specific thresholds
   - US thresholds are global fracture risk 20% or greater or hip fracture risk 3% or greater
Limitations of FRAX

- Underestimates future risk as it only reports risk for hip and major fractures which comprise only half of all fractures
- Underestimates the risk in patients with multiple prior osteoporosis related fractures
- Underestimates the risk in patients with lumbar spine BMD lower than the femoral neck
- Underestimates the risk in patients secondary osteoporosis
- Underestimates the risk in patients in those at high risk of falling
- Only Estimates risk of those who are drug naive
Osteoporosis – Case 1

70 YO Caucasian Female
- PCP ordered a BMD screen – first time measured
- BMD – Lowest measured site in the Fem Neck T-score - 2.2
- She is a smoker and her mother has a history of a hip fracture

QUESTIONS?

1. Does she have osteoporosis?  YES!
2. How should patient be treated?
Q3 Fundamental measures for bone health

- Avoid Excess alcohol intake – limit to two drinks a day or less
- Counsel patients to stop or avoid smoking
- Counsel patients to maintain an active lifestyle including weight-bearing, balance and resistance exercises
  - Improve strength, balance & coordination, Reduce risk of falling
  - Improve joint mobility & flexibility
- Counsel on fall prevention including a Safe environment:
  - Bathroom safety, Rugs and night lights
  - Avoid sedatives, hypotensive agents Walking aids (cane, walker)
- Consider referral to physical therapy
# Calcium Intake

Goal is to get as much as possible form dietary sources, supplementing to achieve the daily goal if necessary.

<table>
<thead>
<tr>
<th>FOOD</th>
<th>CALCIUM</th>
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<th>CALCIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Turnip Greens, ½ cup</td>
<td>100</td>
<td>Plain Yogurt, 8 oz</td>
<td>400</td>
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<tr>
<td>Kale cooked 1 cup</td>
<td>100</td>
<td>Cheese, solid 1.5 oz</td>
<td>300</td>
</tr>
<tr>
<td>Cabbage, 1 cup</td>
<td>75</td>
<td>Sardines, 3 oz</td>
<td>325</td>
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<tr>
<td>Bread Slice</td>
<td>75</td>
<td>Milk, 8 oz</td>
<td>300</td>
</tr>
<tr>
<td>Tortilla, corn &amp; flower</td>
<td>45</td>
<td>Tofu ½ cup</td>
<td>250</td>
</tr>
<tr>
<td>Broccoli ½ cup</td>
<td>25</td>
<td>Cottage Cheese 1 cup</td>
<td>140</td>
</tr>
</tbody>
</table>

Recommended daily intake:
- Age 10-20 1300 mg/day
- Age 20-50 1000 mg/day
- Age > 50 1200 mg/dl

Office of Dietary Supplements, National Institute of Health
Calcium Intake

- The optimal intake and utility of calcium supplements is controversial
  - A Swedish study found both dietary and supplement calcium intake of > 1500 mg per day was associated with an increased mortality
  - A Canadian study of over 9,000 subjects found an increased survival advantage to those taking supplements
- Studies suggest dietary calcium may be preferred over supplements.
- Total calcium intake should not exceed 1500 mg per day

Office of Dietary Supplements, National Institute of Health
http://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/
Vitamin D Recommendations

There is considerable disagreement among experts as the optimal and safe upper doses

Institute of Medicine:

<table>
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<th>Age</th>
<th>Units/day</th>
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<tbody>
<tr>
<td>&lt;50</td>
<td>1000</td>
</tr>
<tr>
<td>&gt;50</td>
<td>1200</td>
</tr>
</tbody>
</table>

Safe Maximum dose: 4,000 u/d

Maintain 25-OH D levels at least 30-50 ng/ml

<table>
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<tr>
<th>FOOD</th>
<th>Vit D</th>
<th>Goal Blood Levels of Vit D</th>
<th>Ng/dl</th>
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</thead>
<tbody>
<tr>
<td>Cod Liver Oil 1 Tbs</td>
<td>1360</td>
<td>Deficiency</td>
<td>&lt;15</td>
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<tr>
<td>Swordfish, 3 oz</td>
<td>566</td>
<td>Insufficiency</td>
<td>15-32</td>
</tr>
<tr>
<td>Salmon, 3 oz</td>
<td>447</td>
<td>Adequate</td>
<td>32-60</td>
</tr>
<tr>
<td>Tuna, 3 oz</td>
<td>154</td>
<td>High</td>
<td>60-150</td>
</tr>
<tr>
<td>Milk, 8 oz</td>
<td>120</td>
<td>Potentially Harmful</td>
<td>&gt;150</td>
</tr>
<tr>
<td>Egg yoke, 1</td>
<td>40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Office of Dietary Supplements, National Institute of Health
http://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/
Other Supplements

- Magnesium may be beneficial in those using proton pump inhibitors or diuretics long term
- Vitamin A, K and phytoestrogen
  - Excessive vitamin A, > 10,000 iu/d, should be avoided as it has been shown to have detrimental effects on bone
  - Data on Vitamin K is inconclusive – not recommended
  - Phytoestrogens/ isoflavones – No evidence of benefit – NOT recommended
- Caffeine – high intake associated with increase fractures
- Protein – Adequate protein intake of ~ 0.8 g/kg/day

Office of Dietary Supplements, National Institute of Health
http://ods.od.nih.gov/factsheets/Calcium-HealthProfessional/
Q5 What Osteoporosis Medications should be used?

1. Approved agents with efficacy to reduce hip, non-vertebral and spine fractures
   1. Alendronate, Residronate, Zolendronate, & Denosumab are appropriate as initial therapy
2. Teriparatide, Abaloparatide, Denosumab, or zolendronate should be considered for patients unable to use oral therapy as initial therapy
3. Denosumab is the agent of choice for patients with CKD
4. Raloxifene or Ibandronate may be appropriate in some cases where patients requiring drugs with spine-specific efficacy
5. Estrogen use for non skeletal benefits will also serve to help prevent postmenopausal bone loss, or 0.45-mg conjugated estrogens/20-mg bazedoxifene combination tablets
6. Calcitonin (increases cancers) and Strontium (increased CV risk) therefore their use is not recommended
# Anti-fracture Efficacy of Current Therapies

## Therapeutic Options for Fracture Prevention in PMO Women

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<tr>
<th>Type of Fracture</th>
<th>Antiresorptive Therapy</th>
<th>Bone Formation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bisphosphonates</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Alendronate</td>
<td>Risedronate</td>
</tr>
<tr>
<td>Vertebral</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Hip</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Non-vertebral†</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Decrease Death</td>
<td>✓</td>
<td></td>
</tr>
</tbody>
</table>

*Based on GRADE A evidence as assessed in the Osteoporosis Canada 2010 Clinical Practice Guidelines for the Diagnosis and Management of Osteoporosis in Canada.

† For postmenopausal women, indicates first-line therapies and Grade A recommendation.
‡ Hormone therapy (estrogen) can be used as first-line therapy in women with menopausal symptoms.
∆ In Clinical trials, non-vertebral fractures are a composite endpoint including hip, femur, pelvis, tibia, humerus, radius, and clavicle.

Fracture Prevention with Zolendronate in Older Women with Osteopenia
Zolendronate Treatment Decrease in Death Rates

Horizon Fracture Trial

Fracture Prevention with Zolendronate in Older Women with Osteopenia

Table 3. Prespecified Adverse Events of Interest.

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N=1000)</th>
<th>Zoledronate (N=1000)</th>
<th>Odds Ratio with Zoledronate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Women with at least one event</td>
<td>Events</td>
</tr>
<tr>
<td></td>
<td>no.</td>
<td>(95% CI)</td>
<td>no.</td>
</tr>
<tr>
<td>Death</td>
<td>41</td>
<td>7.0 (5.4–9.4)</td>
<td>41</td>
</tr>
<tr>
<td>Sudden death</td>
<td>1</td>
<td>0.2 (0.002–0.9)</td>
<td>1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>43</td>
<td>7.3 (5.3–9.8)</td>
<td>39</td>
</tr>
<tr>
<td>Coronary-artery revascularization</td>
<td>32</td>
<td>5.4 (3.7–7.7)</td>
<td>30</td>
</tr>
<tr>
<td>Stroke</td>
<td>22</td>
<td>3.7 (2.3–5.7)</td>
<td>20</td>
</tr>
<tr>
<td>Composite of vascular events*</td>
<td>98</td>
<td>16.6 (13.5–20.3)</td>
<td>69</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>15</td>
<td>2.5 (1.4–4.2)</td>
<td>14</td>
</tr>
<tr>
<td>Cancer†</td>
<td>127</td>
<td>21.5 (18.0–18.1)</td>
<td>121</td>
</tr>
<tr>
<td>Osteonecrosis of the jaw</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>92</td>
<td>15.6 (12.6–19.1)</td>
<td>55</td>
</tr>
</tbody>
</table>

* This category included any of the following events: sudden death, myocardial infarction, coronary-artery revascularization, or stroke.
† This category excluded nonmelanoma skin cancers.
Osteoporosis – Case 1

70 YO Caucasian Female

Plan

1. Begin therapy that will protect against hip and spine fracture
   1. Oral Bisphosphonate Alendronate or Residronate weekly
   2. Zolendronate every 12-18 months if renal function normal, or
   3. Denosumab 60 mg every 6 months

2. Reassess fracture risk every 2-4 years
Osteoporosis – Case 2

63 YO Caucasian F

- This patient present with a new compression fracture
- No history of prior treatment
- Current BMD T-score – 3.1 in the total Femur

QUESTIONS?

1. What is the best choice of therapy?
2. How long should the patient be treated and how should the patient be monitored?
Evaluate for prevalent fracture

- Height loss, Lateral spine x-rays or VFA
- Many vertebral fractures go undetected

Normal (Grade 0)

Wedge fracture

Biconcave fracture

Crush fracture

Mild fracture
(Grade 1, ~20-25%)

Moderate fracture
(Grade 2, ~25-40%)

Severe fracture
(Grade 3, ~40%)

When to consider VFA:
- Women > 70
- Height loss of 1.5 inches
- Self reported fracture or undocumented back pain
- Chronic Steroid therapy

Genant et al., J Bone Miner Res 1993, 8:137
Prior Fracture is the Most Important Risk Factor for another Fractures

Recent Fx suggest very high risk (Osteoporosis Emergency)
- In over 377,000 women the first fracture = absolute risk of another fracture:
  - 10% in the first year, 18% in the first two years and 31% in the first five years after the fractures

1. 1 Vertebral Fracture at Baseline
   - 5 fold increase in vertebral fracture\(^1\)

2. 2 or more Vertebral Fractures at Baseline
   - 12 fold increase in vertebral fracture\(^1\)

3. 1 Symptomatic Vertebral Fracture at Baseline
   - 2 fold increase in hip fracture\(^2\)

\(^2\)Kanis K.A., Osteoporosis and its Consequences, Osteoporosis, Blackwell Science Ltd. p 3
Mechanism of Action of Available Osteoporosis Therapies

Estrogen therapy
Selective estrogen receptor modulators
Hormones

Bisphophonates
Binds to bone; inhibits osteoclasts

Teriparatide
PTH analog

Denosumab
RANK Ligand inhibitor

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<td>Vertebral</td>
<td>6.2 v 3.2 48%</td>
<td>10.9 v 3.3 70%</td>
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<td>7.2 v 2.3 68%</td>
<td>14.3 v 5.0 65%</td>
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<td></td>
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<td>4.2 v 0.6 86%</td>
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*Statistical significance.*
†Non-vertebral fractures.
Comparing Fracture Outcomes
Anabolic vs. Antiresorptive Therapies

Two studies (Fracture Outcomes Not Primary Endpoints)
- In Glucocorticoid Induced Osteoporosis:
  - Teriparatide reduced vertebral fractures by 90% compared to Alendronate
    over 18 months (1)
- In Patients with acute painful vertebral fractures:
  - Teriparatide reduced vertebral fractures by 50% compared to Residronate
    over 1 year (2)

Two Recent Studies Compare Anabolic an Antiresorptive Therapies on Fracture Outcomes as Primary Endpoints
- VERO: Compared Teriparatide to Risedronate (3)
- ARCH: Compared Romosozumab to Alendronate (4)

VERO: Teriparatide vs Risedronate in Severe Osteoporosis

Vertebral Fractures

Incidence of New Vertebral Fractures

<table>
<thead>
<tr>
<th>Patients with New Vertebral Fractures (%)</th>
<th>Teriparatide</th>
<th>Risedronate</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 months</td>
<td>3.1% (18/574)</td>
<td>6.0% (35/585)</td>
</tr>
<tr>
<td>24 months</td>
<td>5.4% (28/516)</td>
<td>12.0% (64/533)</td>
</tr>
</tbody>
</table>

ARR: 6.6%
RRR: 56%
(95% CI: 0.29, 0.68)
p<0.0001
NNT: 15

Hazard Ratio: 0.66
(95% CI: 0.39, 1.10)
P=0.099

Non Vertebral Fractures

Kendler, et al The Lancet 2017
ARCH: Romosozumab vs. Alendronate

Vertebral Fractures

Non Vertebral & Hip Fracture

Saag et al NEJM 2017
Osteoporosis – Case 2

63 YO Caucasian F

- This patient present with a new compression fracture
- No history of prior treatment
- Current BMD T-score – 3.1 in the total Femur

Treatment Plan

1. What is he best choice of therapy?
   1. Anabolic therapy with Teriparatide or Abaloparatide for 18 months
   2. Follow up with antiresorptive: Zolendronate every 12-18 months or denosumab every 6 months
   3. Continue therapy life long
RISK OF OSTEOPOROSIS TREATMENTS
Osteoporosis – Case 3

70 YO Caucasian F

- At age 60 diagnosed with PMO based in BMD T-Score if -2.8 in the hip
- Treated with oral alendronate for last 10 years
- No History of Fracture
- Current BMD T-score – 2.5

QUESTIONS?
1. Should treatment be continued – what is the risk of continued treatment?
2. How should patient be monitored?
### BMD Efficacy of Long-term Treatment*

In long term trials, BMD continues to increase or remains stable

<table>
<thead>
<tr>
<th>Medication</th>
<th>Pivotal Study Extended</th>
<th>Treatment Duration (yrs)</th>
<th># of Participants</th>
<th>% Change Lumbar Spine BMD †</th>
<th>% Change Total Hip BMD †</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risedronate¹</td>
<td>VERT-MN</td>
<td>7</td>
<td>68</td>
<td>11.5</td>
<td>3.9</td>
</tr>
<tr>
<td>Alendronate²</td>
<td>FLEX</td>
<td>10</td>
<td>86</td>
<td>13.7</td>
<td>6.7</td>
</tr>
<tr>
<td>Zoledronic Acid³</td>
<td>HORIZON (Analysis of 9 year study)</td>
<td>9</td>
<td>616</td>
<td>12.1</td>
<td>4.3</td>
</tr>
<tr>
<td>Denosumab⁴</td>
<td>FREEDOM (Analysis 10 year study)</td>
<td>7/10</td>
<td>2343</td>
<td>15.2</td>
<td>7.5</td>
</tr>
</tbody>
</table>

* Not head to head analyses: Results cannot be compared due to differing study populations and methodologies.

† Represents % change from BL of Pivotal Trial.

² Represents 10 mg dose only.

# Safety and Tolerability of Available Treatments

<table>
<thead>
<tr>
<th>Bisphosphonates</th>
<th>Denosumab</th>
<th>Raloxifene</th>
<th>Teriparatide</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypocalcemia*</td>
<td>Hypocalcemia*</td>
<td>Vasodilation</td>
<td>Transient orthostatic hypotension</td>
</tr>
<tr>
<td>GI symptoms†</td>
<td>Infections (serious events 4.1% vs. 3.4% placebo)</td>
<td>Venous thromboembolism (↑ risk vs. placebo)</td>
<td>Osteosarcoma (only observed in animal trials, not clinical trials)</td>
</tr>
<tr>
<td>Postmarketing reports of musculoskeletal pain</td>
<td>Dermal events (10.8% vs. 8.2% placebo)</td>
<td>Lipid and triglyceride monitoring</td>
<td>Urolithiasis §</td>
</tr>
<tr>
<td>Osteonecrosis of jaw‡</td>
<td>Osteonecrosis of jaw‡</td>
<td>Stroke¶</td>
<td></td>
</tr>
<tr>
<td>Atypical Fracture (rare)</td>
<td>Atypical Fracture (rare)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal impairment **</td>
<td>Suppression of bone turnover</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atrial fibrillation (2.5% vs. 1.9% placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Correct with adequate calcium & Vitamin D intake prior to initiating therapy. † Rarely, oral bisphosphonates have been associated with severe esophageal events. ‡ Uncommon; mostly with cancer patients and/or dental procedures. ¶ Consider risk/benefit balance for women with a history of stroke or risk factors for stroke or venous thromboembolism. § Urinary calcium monitoring should be considered for patients with active urolithiasis and hypercalciuria. ** Recommended that all patients have their renal function assessed prior to treatment. Refer to respective Product Monographs for full Prescribing Information.
Osteonecrosis of the Jaw (ONJ)

- **Bisphosphonate-Related Osteonecrosis of the Jaw**
  - **Bisphosphonates:**
    - Oncology patients: 0.7 to 6.7%
    - Osteoporosis Pts: 0.04 to 0.2%
  - **RANK-L inhibitors**
    - 5.2 per 10,000 subject years

- **Risk factors:**
  - Dento-alveolar surgery
  - Steroid therapy
  - Chemotherapy
  - High dose Bisphosphonate
  - Duration of therapy

- **Treatment**
  - Avoid surgical manipulation + Antibiotics
Atypical Sub-trochanteric Femur Fracture

- Ask about new thigh or pelvic pain
- Plain X-ray of the femur best screening tool
- Discontinue antiresorptive

- Consider prophylactic rodding
- Some recommending teriparatide therapy
Atypical Femur Fracture

- Kaiser of Southern California
  - 152,934 women aged 50 or older, members of Kaiser Permanente So Cal between Jan. 1, 2007, and Sept. 30, 2015. There were 185 AFFs overall (incidence rate 1.70 per 10,000 person-years).
  - Relative Risk related to duration of exposure compared to those exposed less than 1 year
    - 1-4 years: 3 X
    - 4 – 8 years: 15 X
    - > 8 years: 37 X

- Discontinuing BP for 4 years reduced AFF rates to pretreatment levels

- Pretreatment BMD showed those with higher BMD had a 40% increase in AFF risk per standard deviation of BMD increase (HR = 1.4; 95% CI, 1.2-1.7).
Increase Hip Fracture with Discontinuation of Therapy

- Older women Analysis of 150,000 Medicare database on bisphosphonate treatment for at least 3 years who then stopped taking the drug Compared to those who never stopped
  - Off drug for 1-2 years showed a 20% increased risk for hip fracture
  - Off drug for 2-3 years showed a 40% increased risk for hip fracture

- The finding seems to dispute a recent recommendation from the American College of Physicians (Ann Intern Med. 2017 June 6;166[11]:818-39) that drug treatment to prevent bone fractures in osteoporotic women should stop after 5 years

- For Every AFF caused, 100 hip and 200 other fractures are PREVENTED by treatment
Osteoporosis: Comparing Risks

<table>
<thead>
<tr>
<th>Event</th>
<th>Risk per 100,000 People per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Fragility Fracture (1)</td>
<td>2668</td>
</tr>
<tr>
<td>Hip Fracture (1)</td>
<td>387</td>
</tr>
<tr>
<td>Anaphylaxis from PCN Shot</td>
<td>32</td>
</tr>
<tr>
<td>Death by MVA</td>
<td>11</td>
</tr>
<tr>
<td>Death by Murder</td>
<td>6</td>
</tr>
<tr>
<td>ONJ- Osteoporosis Patient</td>
<td>0.7</td>
</tr>
<tr>
<td>Death by Lighting Strike in NM</td>
<td>0.6</td>
</tr>
</tbody>
</table>

(1) Women age 65-69 (from Swedish National Bureau of Statistics and database of Olmsted County, MN, USA.)

Recommendations for Long Term Therapy

- **AACE recommends:**
  - **Bisphosphonate holiday or break from these treatments:**
    - In those at moderate risk after 4-5 years of treatment if bone density is stable
    - In those with osteoporosis at high risk—discontinue and after 10 years of stability
    - In those who continue to fracture
      - Evaluate for secondary causes
      - Consider change to anabolic therapy
  - **Elderly patients** and those with very low bone strength should be closely followed during a break from treatment.
  - Resume therapy in those at high risk for fracture after two years of “Bisphosphonate Holiday”

- A Holiday is not recommended for denosumab
  - Discontinuation has been associated with increased risk of multiple Vertebral Fractures

- Always follow anabolic therapy with antiresorptive for at least 1-2 years
Osteoporosis – Case 3

70 YO Caucasian Female

- At age 60 diagnosed with PMO based in BMD T-Score if -2.8 in the hip
- Treated with oral alendronate for last 10 years
- No History of Fracture
- Current BMD T-score – 2.5

Treatment Plan

1. Discontinue bisphosphonate for two years – reassess fracture risk – if at high risk resume treatment
2. If no interval fractures good candidate for zolendronate every 12-18 months for additional 3-5 doses or denosumab every 6 months
3. If Fractures occur anabolic therapy followed by antiresorptive
AACE/ACE 2016 Postmenopausal Osteoporosis Treatment Algorithm

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5, a history of fragility fracture, or high FRAX® fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

No prior fragility fractures or moderate fracture risk**

- Alendronate, denosumab, risedronate, zoledronic acid***
- Alternate therapy: Ibendronate, raloxifene

Reassess at least yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to teriparatide if on injectable antiresorptive or at very high risk of fracture

Prior fragility fractures or indicators of higher fracture risk**

- Denosumab, teriparatide, zoledronic acid***
- Alternate therapy: Alendronate, risedronate

Reassess at least yearly for response to therapy and fracture risk

Decreasing BMD and fractures

Denosumab

Continue therapy or consider adding teriparatide if progression of bone loss or recurrent fractures

Sequential therapy with oral or injectable antiresorptive agent

- If stable, continue therapy for 6 years****
- If progression of bone loss or recurrent fractures, consider switching to teriparatide

Zoledronic acid

Teriparatide for up to 2 years

- If stable, continue therapy for 6 years****
- If progression of bone loss or recurrent fractures, consider switching to teriparatide

Note:
- 10 year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%. Non-US countries/regions may have different thresholds.
- Indicators of higher fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.
- Medications are listed alphabetically.
- **** Consider a drug holiday after 6 years of IV zoledronic acid. During the holiday, another agent such as teriparatide or raloxifene could be used.

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